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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,655	11/30/2004	Hans Groenlund	LNK-031	9022

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EXAMINER	
ROONEY, NORA MAUREEN	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,655	GROENLUND ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,15 and 17-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 15, 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/02/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/02/2009 has been entered.

2. Claims 10, 15 and 17-24 are currently under examination as they read on a microparticle comprising a bead and a plant pollen allergen.

3. Applicant's IDS document filed on 03/02/2009 is acknowledged.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10, 15 and 17-24 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for : a microparticle consisting essentially of Phl p 5b covalently bound to Cyanogen bromide-activated spherical Sepharose particles (CBP) and a medicament thereof, does not provide reasonable enablement for : **a medicament for allergen-**

specific immunotherapy capable of inducing strong antibody responses with less granulomatous tissue reactions, said medicament containing a therapeutically effective amount of **microparticles** in a pharmaceutical formulation, said **microparticles** consisting essentially of: (a) **a bead consisting of three-dimensionally cross-linked agarose**; and (b) **a purified recombinant polypeptide allergen derived from plant pollen** bound to said bead by means of a covalent bond between said cross-linked agarose and a reactive group of **said allergen** of claim 15; wherein **the allergen is derived from grass pollen** of claim 18; wherein **the grass pollen allergen** is **derived from timothy grass pollen** of claim 19 and as applied to claims 10, 16-17 and 20-23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons as set forth in the Office Action mailed on 10/30/2008.

In addition, the specification does not adequately disclose a medicament for allergen specific immunotherapy capable of inducing "strong antibody responses with less granulomatous tissue reactions." First, the term "strong" is not specific enough to convey to one of ordinary skill in the art what is meant by it. In addition, the term encompasses all antibody responses, including antibody responses that increase IgE and exacerbate the allergic response. The specification has not adequately disclosed a medicament for allergen-specific immunotherapy that induces a strong IgE response. Further, the term "less" is a term of degree that is not defined within the claim. The specification discloses medicaments that induce less granulomatous tissue reactions than alum-based adjuvants, but that is not a limiting definition within the specification nor is that limitation recited in the claims. Therefore, the claims read on a medicament that

induces less granulomatous tissue reactions than any medicament. The specification has not adequately disclosed such a genus of microparticles.

Further, the bead may not "consist" of three dimensionally cross-linked carbohydrate agarose because the allergen must be coupled to its surface by cyanogen activated bromide. A bead may not consist of agarose and further comprise cyanogen activated bromide.

Applicant's arguments filed on 03/02/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "As mentioned previously, the medicaments of the present invention operate in a manner analogous to conventional Alum-adsorbed allergy vaccines by inducing allergen-specific IgG responses similar to those of Alum-based particles[2] Accordingly, one of ordinary skill in the art would be well versed in the methods of making and using the medicaments of the present invention, without undue experimentation and with predictable results. Furthermore, Applicants have conclusively demonstrated herein that the microparticles of the present invention are capable of inducing strong IgG1, IgG2a/b, and IgG3 antibody responses in mice, antibodies referred to in the art as "blocking antibodies" for their ability to prevent contact between the allergen and the IgE molecules present in the allergic patient's body, thereby avoiding mast cell- and basophil-mediated allergic responses such as cytokine secretion and histamine release,[3] with minimal negative side effects (like the granulomatous tissue reaction), with predictable efficacy of adsorption, with predictable stability of adsorbents, and without altering the functionality of the bound allergen. Thus, it is readily apparent that the medicaments of the instant invention are suited to allergen-specific immunotherapy and are capable of "inducing strong antibody responses with less granulomatous tissue reactions" as the pending claims now require. Thus, Applicants respectfully submit that the scope of the pending claims is commensurate with the admitted scope of enablement. Applicants further submit that the remaining allegations of undue unpredictability and criticality fall with this primary one. Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.
>
> With regard to the remaining issues of items (b) - (d), Applicants reiterate that the present invention relates to the discovery of the advantageous nature of carbohydrate-based allergen particles (CBPs) over traditional metal-based allergen particles (like aluminum hydroxide and iron oxide particles) in the context of allergen-specific immunotherapy. Applicants respectfully submit that this novel finding is not restricted to a specific carbohydrate or specific polypeptide allergen or even a specific size range. Contrary to the Examiner's

suggestion, the improved "allergen specific non-responsiveness" and "high density" coupling associated with the medicaments of the present invention and observed by Neimert-Andersson et al. in the Allergy, 2008 reference arises more from the selection of carbohydrate over metal and covalent binding over chemical adsorption that any other factor.

Applicants further submit that the principle mode of allergen-specific immunotherapy does not depend on the nature of the particular allergen but can be readily and routinely generalized for other peptide allergens. In addition, as noted in the instant specification and in the prior responses, the covalent coupling of purified recombinant polypeptide allergens to carbohydrate-based particles, such as agarose/sepharose beads, uses well-described and reproducible procedures analogous to those conventional in the art of ELISA-based diagnostic protocols. Thus, in the context of the instant invention, the timothy grass pollen allergen Phl p 5b (SEQ ID NO: 1) is indeed representative of the requisite structural and functional properties of the genus of "purified recombinant polypeptide allergens derived from plant pollen". As for the supporting carbohydrate bead, to expedite prosecution, Applicants have amended the claims to require the bead to consist of three-dimensionally cross-linked agarose. Thus, Applicants respectfully submit that the claimed genus of microparticles is adequately described and enabled by the teachings of the instant specification coupled with the knowledge in the art.

In sum, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification demonstrate that a reasonable correlation exists between the scope of the claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the claims 10 and 15-23 without undue experimentation and with a reasonable expectation of success. Applicants further submit that the instant specification provides an adequate written description of the genus of medicaments encompassed by claims 10, 15, and 17-24, so as to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention now claimed. Accordingly, Applicants respectfully petition for the reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. § 112, first paragraph. "

It remains the Examiner's position that the specification has not adequately disclosed a medicament for allergen-specific immunotherapy capable of inducing strong antibody responses with less granulomatous tissue reactions for the genus of microparticles and pharmaceutical compositions encompassed by the instant claim recitations. The specification does not adequately disclose a medicament comprising bead consisting of "three dimensionally cross-linked carbohydrate agarose." The specification only disclosed 2 µm cyanogen bromide-activated spherical Sepharose particles (CBP) for use in the claimed invention. Gronlund et al. (PTO-892 mailed 02/21/2008; Reference W) teaches that coupling to cyanogen bromide-activated spherical Sepharose is important because a covalent bond forms between the particle

and the antigen, thus reducing anaphylactic reactions, without altering the immunological properties of the antigen and because the beads are bio-compatible (In particular, page 527, whole document). The art of Neimert-Anderson et al. (PTO-892; Reference U) teaches that allergen specific non-responsiveness is induced by 2 μm CBP particles because the allergens can be coupled to the CBPs with a high density and the size allows it to be efficiently phagocytosed by antigen presenting cells (In particular, 'Discussion' section on page 525, whole document). Therefore, not only is the type of particle used important for generation of non-responsiveness, but the size of the particle matters as well. Applicant argues that "the improved "allergen specific non-responsiveness" and "high density" coupling associated with the medicaments of the present invention and observed by Neimert-Andersson et al. in the Allergy, 2008 reference arises more from the selection of carbohydrate over metal and covalent binding over chemical adsorption that any other factor." However, Applicant provides no data to support this contention and this contention is contrary to the teachings of the Neimert-Andersson et al. and Gronlund et al. references of record. It is noted that the arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 The specification has not adequately disclosed the genus of medicaments encompassed by the instant claims recitation for use in the claimed invention, especially in view of the post-dated art which demonstrates that the properties of the particle are important for generation of non-responsiveness.

The art of Neimert-Anderson et al., of record, with common authorship to the instant inventors and published in 2008 also teaches "we show for the first time that CBPs modulate the

immune response, allergic inflammation and AHR when use in the treatment of rFel d 1 sensitized mice." Therefore, contrary to Applicant's assertion, one of ordinary skill in the time of invention would not have been "well versed in the methods of making and using the medicaments of the present invention, without undue experimentation and with predictable results." Allergen-specific immunotherapy is complex and unpredictable with possible serious side effects including anaphylactic shock. The specification has demonstrated in mice that one particular pollen allergen may be used to induce antibody responses with less granulomatous tissue reactions. However, the specification does not adequately show, nor does the state of the art teach, that the genus of purified recombinant plant pollen polypeptide allergens coupled to any agarose bead may be used in a medicament for allergen-specific immunotherapy.

6. Claims 10, 15 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: a microparticle consisting essentially of Phl p 5b covalently bound to Cyanogen bromide-activated spherical Sepharose particles (CBP) and a medicament thereof.

Applicant is not in possession of: **a medicament for allergen-specific immunotherapy capable of inducing strong antibody responses with less granulomatous tissue reactions,** said medicament containing a therapeutically effective amount of **microparticles** in a

pharmaceutical formulation, said **microparticles** consisting essentially of: (a) **a bead consisting of three-dimensionally cross-linked agarose**; and (b) **a purified recombinant polypeptide allergen derived from plant pollen** bound to said bead by means of a covalent bond between said cross-linked agarose and a reactive group of **said allergen** of claim 15; wherein **the allergen is derived from grass pollen** of claim 18; wherein **the grass pollen allergen** is **derived from timothy grass pollen** of claim 19 and as applied to claims 10, 16-17 and 20-23 for the same reasons as set forth in the Office Action mailed on 10/30/2008.

Applicant has disclosed only a microparticle consisting essentially of Phl p 5b covalently bound to CBP and a medicament thereof; therefore, the skilled artisan cannot envision all the contemplated microparticle and medicament possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

Applicant's arguments filed on 03/02/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "As mentioned previously, the medicaments of the present invention operate in a manner analogous to conventional Alum-adsorbed allergy vaccines by inducing allergen-specific IgG responses similar to those of Alum-based particles[2] Accordingly, one of ordinary skill in the art would be well versed in the methods of making and using the medicaments of the present invention, without undue experimentation and with predictable results. Furthermore, Applicants have conclusively demonstrated herein that the microparticles of the present invention are capable of inducing strong IgG1, IgG2a/b, and IgG3 antibody responses in mice, antibodies referred to in

the art as "blocking antibodies" for their ability to prevent contact between the allergen and the IgE molecules present in the allergic patient's body, thereby avoiding mast cell- and basophil-mediated allergic responses such as cytokine secretion and histamine release,[3] with minimal negative side effects (like the granulomatous tissue reaction), with predictable efficacy of adsorption, with predictable stability of adsorbents, and without altering the functionality of the bound allergen. Thus, it is readily apparent that the medicaments of the instant invention are suited to allergen-specific immunotherapy and are capable of "inducing strong antibody responses with less granulomatous tissue reactions" as the pending claims now require. Thus, Applicants respectfully submit that the scope of the pending claims is commensurate with the admitted scope of enablement. Applicants further submit that the remaining allegations of undue unpredictability and criticality fall with this primary one. Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

With regard to the remaining issues of items (b) - (d), Applicants reiterate that the present invention relates to the discovery of the advantageous nature of carbohydrate-based allergen particles (CBPs) over traditional metal-based allergen particles (like aluminum hydroxide and iron oxide particles) in the context of allergen-specific immunotherapy. Applicants respectfully submit that this novel finding is not restricted to a specific carbohydrate or specific polypeptide allergen or even a specific size range. Contrary to the Examiner's suggestion, the improved "allergen specific non-responsiveness" and "high density" coupling associated with the medicaments of the present invention and observed by Neimert-Andersson et al. in the Allergy, 2008 reference arises more from the selection of carbohydrate over metal and covalent binding over chemical adsorption that any other factor.

Applicants further submit that the principle mode of allergen-specific immunotherapy does not depend on the nature of the particular allergen but can be readily and routinely generalized for other peptide allergens. In addition, as noted in the instant specification and in the prior responses, the covalent coupling of purified recombinant polypeptide allergens to carbohydrate-based particles, such as agarose/sepharose beads, uses well-described and reproducible procedures analogous to those conventional in the art of ELISA-based diagnostic protocols. Thus, in the context of the instant invention, the timothy grass pollen allergen Phl p 5b (SEQ ID NO: 1) is indeed representative of the requisite structural and functional properties of the genus of "purified recombinant polypeptide allergens derived from plant pollen". As for the supporting carbohydrate bead, to expedite prosecution, Applicants have amended the claims to require the bead to consist of three-dimensionally cross-linked agarose. Thus, Applicants respectfully submit that the claimed genus of microparticles is adequately described and enabled by the teachings of the instant specification coupled with the knowledge in the art.

In sum, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification demonstrate that a reasonable correlation exists between the scope of the claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the claims 10 and 15-23 without undue experimentation and with a reasonable expectation of success. Applicants further submit that the instant specification provides an adequate written description of the genus of medicaments encompassed by claims 10, 15, and 17-24, so as to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention now claimed. Accordingly, Applicants respectfully petition for the reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. § 112, first paragraph. "

As stated *supra*, the bead may not "consist" of three dimensionally cross-linked

carbohydrate agarose because the allergen must be coupled to its surface by cyanogen activated bromide. A bead may not consist of agarose and further comprise cyanogen acitvated bromide.

It remains the Examiner's position that the specification has not adequately described a medicament for allergen-specific immunotherapy capable of inducing strong antibody responses with less granulomatous tissue reactions for the genus of microparticles and pharmaceutical compositions encompassed by the instant claim recitations. The specification does not adequately describe a medicament comprising a bead "consisting of three dimensionally cross-linked carbohydrate agarose." The specification only disclosed 2 μm cyanogen bromide-activated spherical Sepharose particles (CBP) for use in the claimed invention. The specification has not adequately described the genus of medicaments encompassed by the instant claims recitation for use in the claimed invention, especially in view of the post-dated art which demonstrates that the properties of the particle are important for the claimed function as an allergen-specific immunotherapy medicament. The specification has described in mice that one particular pollen allergen may be used to induce antibody responses with less granulomatous tissue reactions. However, the specification does not adequately describe, nor does the state of the art teach, that the genus of any purified recombinant plant pollen polypeptide allergen coupled to any agarose bead may be used in a medicament for allergen-specific immunotherapy.

Accordingly, the specification has not adequately described a correlation between the structure of the polypeptide allergen and agarose bead such that the combination can be used to generate in a medicament for allergen-specific immunotherapy capable of inducing strong

antibody responses with less granulomatous tissue reactions *in vivo*. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" Ex parte *Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007)), at page 16. In this instant case, Applicants have not provided sufficient guidance as to what polypeptide allergens can be combined with what agarose beads to result in a medicament for allergen-specific immunotherapy capable of inducing strong antibody responses with less granulomatous tissue reactions. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17. In the instant case, definition by function (capable of inducing strong antibody responses with less granulomatous tissue reactions) does not suffice to define the genus of medicaments encompassed because it is only an indication of what the medicament does rather than what it is.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 26, 2009

Nora M. Rooney

Patent Examiner

Technology Center 1600

/Nora M Rooney/
Examiner, Art Unit 1644